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| APPLICATION NO: | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/976,961 | 10/12/2001 | Keith L. Black | 18810-80367 | 3007 |

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EXAMINER

FETTEROLF, BRANDON J

| ART UNIT | PAPER NUMBER |
|----------|--------------|
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1642

DATE MAILED: 08/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/976,961

Applicant(s)

BLACK ET AL.

Examiner

Brandon J. Fetterolf, PhD

Art Unit

1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 16 May 2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-45 is/are pending in the application.
- 4a) Of the above claim(s) 4-6, 14-16, 22-24 and 35-37 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 3, 7-13, 17-21 and 25-32 is/are rejected.
- 7) ☒ Claim(s) 2, 33-34 and 38-45 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

Art Unit: 1642

Black et al.

Response to the Amendment

The Amendment filed on 05/16/2005 in response to the previous Non-Final Office Action (01/13/2005) is acknowledged and has been entered.

Claims 1-45 are currently pending.

Claims 4-6, 14-16, 22-24 and 35-37 are withdrawn from consideration as being drawn to non-elected inventions.

Claims 1-3, 7-13, 17-21, 25-34 and 38-45 are currently under consideration.

The Declaration Under CFR 1.132 filed on 05/16/2005 by the inventor, Keith L. Black is acknowledged and has been considered. It is noted however, that the exhibit referred to as "Exhibit A" does not appear to be present in Application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Objections Maintained:

Claims 1-2, 7-12, 17-20, 25-33 and 38-45 remain objected to because claims 1, 8, 17 and 33 are drawn to a genus of calcium-activated potassium channel activators.

Rejections Maintained:

Claims 1, 3, 7-13, 17-21 and 25-32 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for inducing apoptosis or inhibiting the growth/proliferation of a glioma cell or tumor comprising administering a calcium-activated potassium channel activator, wherein the calcium-activated potassium channel activator is NS-1619, does not reasonably provide enablement for a method for inhibiting the proliferation or inducing apoptosis of any malignant cell or tumor by administering a calcium-activated potassium channel

Art Unit: 1642

activator for the reasons of record in the prior Office Action (01/13/20054, pages 4-6) and for the reasons set forth below.

In reference to the previous action which held that the instant specification is not enabling for claims drawn to inducing apoptosis or inhibiting the proliferation or growth of any and all malignant cells or tumors by administering a calcium-activated potassium channel activator, wherein the calcium-activated potassium channel activator is NS-1619, Applicants submit (Remarks, page 9-10) that the method of the present invention is applicable to a wide variety of malignant cells and tumors. For example, Applicants contend that immunohistochemical results establishing over-expression of K_{Ca} channels in glioma-bearing rat brain sections are consistent with results showing that activation of K_{Ca} channels by K_{Ca} activator (NS-1619) selectively induced apoptosis in malignant cells compared to normal cells. Applicants further assert that over-expression of K_{Ca} channels are not limited to just glioma cells or glial tumors, but are found on metastatic tumors of diverse origin, as established in the Declaration of Keith L. Black, including both breast and lung metastatic tumors. Applicants further argue that none of the references cited by the Examiner in support of the enablement rejection teach the role of K_{Ca} channels in apoptosis. Applicants assert that the references relate to other types of potassium channels distinct from calcium-activated potassium channels or teach that activators of these types of potassium channels prevent or induce apoptosis. Therefore, the contrary and varied effects observed in these studies indicate that the role of even non- KCa potassium channels was unclear at the time the application was filed.

As noted above, Applicants have filed a Declaration Under CFR 1.132 by the inventor, Keith L. Black, for support of K_{Ca} channels being over-expressed in tissues other than glioma cells or glial tissues. Dr. Black states (page 3, 24) " K_{Ca} channels are over-expressed on metastatic brain tumors of diverse origin." Specifically, Dr. Black teaches (page 3, 26) that metastasized brain cancer cells originating from breast and lung cancers have high levels of K_{Ca} channels, wherein approximately 60-70% of the cells in the metastatic breast cancer specimens were positive, while approximately 50% of the cells in the lung cancer specimens were positive.

These arguments, as well as the declaration filed by Dr. Black, have been carefully considered, but are not found persuasive.

First, the previous rejection was based on whether the specification, as originally filed, enabled any person skilled in the art to make and/or use the invention commensurate in scope with

Art Unit: 1642

these claims, e.g., a method of inducing apoptosis or inhibiting the proliferation/growth of any and all malignant cells/tumors by administering a calcium-activated potassium channel activator in an amount to induce apoptosis. Thus, while Applicants contend, as evidenced by the Dr. Black Declaration, that K_{Ca} channels are present in metastatic tumors of diverse origin, Applicants have not addressed whether the administration of a calcium-activated potassium channel activator such as NS-1619 will induce apoptosis in any and/or all malignant cells or tumors. Therefore, any argument pertaining to over-expression of a K_{Ca} channels in various tumors is not pertinent because the question is not which cells express K_{Ca} channels, but whether the administration of a calcium-activated potassium channel activator such as NS-1619 will induce apoptosis in any and/or all malignant cells. For example, Wang et al. (Am. J. Physiol. Heart Cir. Physiol. 2004; 287: H2070-H2077) teaches that it is logical to speculate that opening of mito K_{Ca} channels by NS1619 may result in a similar protection against apoptosis as was shown with diazoxide (page H2075, 2nd column, 3rd paragraph). Thus, while Wang *et al.* does not specifically teach malignant cells, Wang *et al.* clearly suggests an alternative effect on apoptosis upon the administration of NS1619. Regarding Applicants contention that none of the references cited by the Examiner in support of the enablement rejection teach the role of K_{Ca} channels in apoptosis, the purpose of these references was not to specifically teach the role of K_{Ca} channels in apoptosis, but instead to show the unpredictability of potassium channels as being the sole mechanism involved in apoptosis in any and all malignant cells or tumors. For example, as stated by Applicants, "the contrary and varied effects observed in these studies indicate that the role of even these non- K_{Ca} potassium channels was unclear at the time the application was filed. More importantly, no role of K_{Ca} channels in apoptosis, or their modulation by K_{Ca} activators to induce apoptosis, is suggested." Thus, how is any person skilled in the art to make and/or use the invention commensurate in scope with these claims, if the prior art does not suggest a role of K_{Ca} channels in apoptosis or their modulation by K_{Ca} activators to induce apoptosis. Consequently, claims 1, 3, 7-13, 17-21 and 25-32 remain rejected under 35 U.S.C. 112, first paragraph.

New Objections:

Claim Objections

Claims 3, 13, 21 and 34 are objected to because of the following informalities: The calcium-activated potassium channel activator, 1,3-dihydro-1-[2-hydroxy-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-2H-benzimidazole-2-one, recited in claims 3, 13, 21 and 34 appears to be misspelled. The appropriate spelling should be 1,3-dihydro-1-[2-hydroxy-5-(trifluoromethyl)phenyl]-5-(trifluoromethyl)-2H-benzimidazole-2-one (see specification, page 10, lines 16-17). Appropriate correction is required.

All other rejections and/or objections are withdrawn in view of applicant's amendments and arguments there to.

The following prior art is provided and made of record (although not relied upon) is considered pertinent to applicant's disclosure:

Bamdad et al. (US 2003/0036199, 5/7/2001) discloses a method of treating a subject having cancer characterized by aberrant expression of MUC1, comprising administering to the subject NS 1619 in an amount effective to reduce tumor growth, e.g. inhibits cellular proliferation (page 16, paragraph 0146). The reference does not specifically teach that the compound induces apoptosis.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Art Unit: 1642

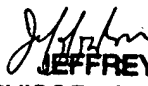
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 8:30 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Brandon J Fetterolf, PhD
Examiner
Art Unit 1642

BF


JEFFREY SIEW
SUPERVISORY PATENT EXAMINER
8/6/05